Holland · Frei Cancer Medicine e.5. American Cancer Society 2000 B.C. Decker Inc

In carcinomas such as colon and lung cancer, the initiation of neoplasia has been shown to involve oncogene and tumor suppressor gene mutations.[151] These mutations are generally thought to result from chemical carcinogenesis, especially in the case of tobacco-related lung cancer, where a novel tumor suppressor gene (designated FHIT) has been found to be inactivated in the majority of cancers, particularly in those from smokers.[152,153] In preneoplastic adenomas of the colon, the K-*ras* gene is often mutated.[32,154] Progression of colon adenomas to invasive carcinoma frequently involves inactivation or loss of the *DCC* and *p53* tumor suppressor genes. Gene amplification is often seen in the progression of some carcinomas and other types of tumors. Amplification of the *erb B-2* oncogene may be a late event in the progression of breast cancer.[100] Members of the *myc* oncogene family are frequently amplified in small cell carcinoma of the lung.[99] As mentioned previously, amplification of N-*myc* strongly correlates with the progression and clinical stage of neuroblastoma.[98] Although there is variability in the pathways of human tumor initiation and progression, studies of various types of malignancy have clearly confirmed the multistep nature of human cancer.

SUMMARY AND CONCLUSIONS

The initiation and progression of human neoplasia is a multistep process involving the accumulation of genetic changes in somatic cells. These genetic changes then consist in the activation of cooperating oncogenes and the inactivation of tumor suppressor genes, which both appear necessary for a complete neoplastic phenotype. Oncogenes are altered versions of normal cellular genes called proto-oncogenes. Proto-oncogenes are a diverse group of genes involved in the regulation of cell growth. The functions of proto-oncogenes include growth factors, growth factor receptors, signal transducers, transcription factors, and regulators of programmed cell death. Proto-oncogenes may be activated by mutation, chromosomal re-arrangement, or gene amplification. Chromosomal re-arrangements that include translocations and inversions can activate proto-oncogenes by deregulation of their transcription (e.g., transcriptional activation) or by gene fusion. Tumor suppressor genes, which also participate in the regulation of normal cell growth, are usually inactivated by point mutations or truncation of their protein sequence coupled with the loss of the normal allele.

The discovery of oncogenes represented a breakthrough for our understanding of the molecular and genetic basis of cancer. Oncogenes have also provided important knowledge concerning the regulation of normal cell proliferation, differentiation, and programmed cell death. The identification of oncogene abnormalities has provided tools for the molecular diagnosis and monitoring of cancer. Most important, oncogenes represent potential targets for new types of cancer therapies. It is more than a hope that a new generation of chemotherapeutic agents directed at specific oncogene targets will be developed. The goal of these new drugs will be to kill cancer cells selectively while sparing normal cells. One promising approach entails using specific oncogene targets to trigger programed cell death. One example of the accomplishment of such a goal is represented by the inhibition of the tumor-specific tyrosine kinase bcr/abl in CML.[155] Our rapidly expanding knowledge of the molecular mechanisms of cancer holds great promise for the development of better combined methods of cancer therapy in the near future.

REFERENCES

1. Levine AJ. The genetic origins of neoplasia. JAMA 1995;273:592.
2. Cooper GM. Oncogenes. Boston: Jones and Barlett, 1990.
3. Bishop JM. Retroviruses and oncogenes II. In: Les Prix Nobel. Stockholm: Almqvist and Wiksell, 1989. p.220–238.
4. Varmus HE. Retroviruses and oncogenes I. In: Les Prix Nobel. Stockholm: Almqvist and Wiksell, 1989. p.194–212.
5. Varmus H. An historical overview of oncogenes. In: Weinberg RA, editor. Oncogenes and the molecular origins of cancer. Cold Spring Harbor (NY): Cold Spring Harbor Laboratory Press; 1989. p.3–44.
6. Bishop JM. Oncogenes and clinical cancer. In: Weinberg RA, editor. Oncogenes and the molecular origins of cancer. Cold Spring Harbor (NY): Cold Spring Harbor Laboratory Press; 1989. p.327–358.
7. Fearon ER. Tumor suppressor genes. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. McGraw-Hill Companies, Inc.; 1998. p.229–236.
8. Boland CR. Hereditary nonpolyposis colorectal cancer. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. McGraw-Hill Companies, Inc.; 1998.
9. Varmus HE. Retroviruses. Science 1988;240:1427–1435.
10. Varmus HE. Form and function of retroviral proviruses. Science 1982;216:812–820.
11. Rous P. A sarcoma of the fowl transmissible by an agent separable from the tumor. J Exp Med 1911;13:397–411.
12. Duesberg PH, Vogt PK. Differences between the ribonucleic acids of transforming and nontransforming avian tumor viruses. Proc Natl Acad Sci USA 1970;67: 1673–1680.
13. Martin GS. Rous sarcoma virus: a function required for the maintenance of the transformed state. Nature 1970;227:1021–1023.
14. Vogt PK. Spontaneous segregation of nontransforming viruses from the cloned sarcoma viruses. Virology 1971;46:939–946.
15. Stehlin D, Varmus HE, Bishop JM, Vogt PK. DNA related to the transforming gene(s) of avian sarcoma viruses is present in normal avian DNA. Nature 1976: b260:170–173.
16. Nusse R, Berns KI. Cellular oncogene activation by insertion of retroviral DNA: genes identified by provirus tagging. In: Klein G, editor. Cellular oncogene activation. New York: Marcel Dekker; 1988. p.95–120.
17. Hayward WS, Neel BG, Astrin SM. Activation of a cellular onc gene by promoter insertion in ALV-induced lymphoid leukosis. Nature 1981;290:475–480.
18. Neel BG, Hayward WS, Robinson HL, et al. Avian leukosis virus-induced tumors have common proviral integration sites and synthesize discrete new RNAs: oncogenesis by promoter insertion. Cell 1981;23:323–334.
19. Payne GS, Bishop JM, Varmus HE. Multiple arrangements of viral DNA and an activated host oncogene in bursal lymphomas. Nature 1982;295:209–214.
20. Robinson HL, Gagnon GC. Patterns of proviral insertion and deletion in avian leukosis virus-induced lymphomas. J Virol 1986;57:28–36.
21. Fung Y-KT, Lewis WG, Crittenden LB, Kung H-J. Activation of the cellular oncogene *c-erbB* by LTR insertion: molecular basis for induction of erythroblastosis by avian leukosis virus. Cell 1983;33:357–368.
22. Kamps MR, Smith RE, Hayward WS. Rapid induction of B-cell lymphomas: insertional activation of *c-myb* by avian leukosis virus. J Virol 1988;62:1423–1432.
23. Morishita K, Parker DS, Mucenski ML, et al. Retroviral activation of a novel gene encoding a zinc finger protein in IL-3 dependent myeloid leukemia cell lines. Cell 1988;54:831–840.
24. Shih C, Shilo B-Z, Goldfarb MP, et al. Passage of phenotypes of chemically transformed cells via transfection of DNA and chromatin. Proc Natl Acad Sci U S A 1979;76:5714–5718.
25. Krontiris TG, Cooper GM. Transforming activity of human tumor DNAs. Proc Natl Acad Sci U S A 1981;78:1181–1184.
26. Murray MJ, Shilo B-Z, Shih C, et al. Three different human tumor cell lines contain different oncogenes. Cell 1981;25:355–361.
27. Perucho M, Goldfarb M, Shimizu K, et al. Human tumor derived cell lines contain common and different transforming genes. Cell 1981;27:467–476.
28. Pulciani S, Santos E, Lauver AV, et al. Oncogenes in human tumor cell lines: molecular cloning of a transforming gene from human bladder carcinoma cells. Proc Natl Acad Sci U S A 1982;79:2845–2849.
29. Parada LF, Tabin CJ, Shih C, Weinberg RA. Human EJ bladder carcinoma oncogene is homologue of Harvey sarcoma virus *ras* gene. Nature 1982;297:474–478.
30. Hahn WC, Counter CM, Lundberg AS, et al. Creation of human tumor cells with defined genetic elements. Nature 1999;400:464–468.
31. Shimizu K, Goldfarb M, Suard Y, et al. Three human transforming genes are related to viral *ras* oncogenes. Proc Natl Acad Sci U S A 1983;80:2112–2116.
32. Bos JL. *Ras* oncogenes in human cancer: a review. Cancer Res 1989;49:4682–4689.
33. Bargmann CI, Hung M-C, Weinberg RA. Multiple independent activations of the *neu* oncogene by a point mutation altering the transmembrane domain of p185. Cell 1986;45:649–657.
34. Park M, Dean M, Cooper CS, et al. Mechanism of *met* oncogene activation. Cell 1986;45:895–904.
35. Takahashi M, Ritz J, Cooper GM. Activation of a novel human transforming gene, *ret*, by DNA rearrangement. Cell 1985;42:581–588.
36. Fusco A, Grieco M, Santoro M, et al. A new oncogene in human thyroid papillary carcinomas and their lymph-nodal metastases. Nature 1987;328:170–172.
37. Grieco M, Santoro M, Berlingieri MT, et al. PTC is a novel rearranged form of the ret proto-oncogene and is frequently detected in vivo in human thyroid papillary carcinomas. Cell 1990;60:557–563.
38. Croce CM. Role of chromosome translocations in human neoplasia. Cell 1987;49:155–156.
39. Rowley JD. Recurring chromosome abnormalities in leukemia and lymphoma. Semin Hematol 1990;27:122–136.
40. Nowell PC, Hungerford D. A minute chromosome in human granulocytic leukemia. Science 1960;132:1497.
41. Nowell PC. Cytogenetic approaches to human cancer genes. FASEB J 1994;8: 408–413.
42. Cross M, Dexter TM. Growth factors in development, transformation, and tumorigenesis. Cell 1991;64:271–280.
43. Weinberg RA. Growth factors and oncogenes. In: Weinberg RA, editor. Oncogenes and the molecular origins of cancer. Cold Spring Harbor (NY): Cold Spring Harbor Laboratory Press; 1989. p.45–66.